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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/813,760	BERNSTEIN, JOEL E.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/31/04 and Tele. Interview on 11/08/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *16-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/22/05, 05/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-29, drawn to a composition comprising one or more of hepatotoxic compound, methionine and nicotinamide.

II. Claims 30-37, drawn to a method of using said composition.

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the process for using the product as claimed can be practiced with another materially different products, for example sterol compound (US 5198432 and US 5336485), hepatocyte growth factor (US 5703048), organosulfur compound (US 5474757) and extract of plant Cryptolepis Buchanani (US 6686375).

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

2. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend**

from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

3. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species (e.g., acetaminophen) from hepatotoxic compound under the instant claims of the elected Group.

Moreover, whatever specific compound is ultimately elected, applicants are required to list all claims readable thereon.

With the election of a specific exemplified compound, a generic concept will be identified by the examiner as the inventive group for examination.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

4. During a telephone conversation with Alice Martin (Barnes & Thornburg LLP) on November 08, 2006 a provisional election was made with traverse to prosecute the invention of Group I which is drawn to a composition along with acetaminophen as the elected species. Affirmation of this election must be made by applicant in replying to this Office action.

5. Claims 1-15 read on the elected invention. Claims 16-37 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Objections

6. Claim 13 is objected to because of the following informalities: Misspelling of "flucanozole" is present. "flucanozole" should be corrected as "fluconazole".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-12 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for the specific hepatotoxic compound such as acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium and valproic acid, does not reasonably provide enablement for "a hepatotoxic compound". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; the breadth of the claims; the amount of direction or guidance presented; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The present invention is drawn to a composition one or more of hepatotoxic compound, about 5mg to about 500 mg of methionine and about 10mg to about 500mg of nicotinamide.

The interpretation of the instant claims allows for the inclusion of any known hepatotoxic compound or drug that are known to exist and those that may be discovered in the future.

The relative skill of the artisan and the unpredictability of the pharmaceutical art is very high. To practice the instant invention to the claimed scope, applicant would have to (i) screen numerous possible compounds characterized as "hepatotoxic compound, (ii) assay to find out

which compounds are able to induce hepatotoxicity at what concentration level and then (iii) extrapolate the test and result to the claimed invention. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)), the skilled artisan would have not known how to extrapolate the examples provided in the instant specification ("acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium and valproic acid" are set forth as suitable working examples) to the larger and highly varied genera of compounds that are characterized by "hepatotoxic compound", without undue amount of experimentation.

As discussed above, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art, and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to make/use the claimed "hepatotoxic compound" that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction

in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Summers (US 6733797 B1).

Summers teaches a composition comprising chromium or curcuma (which is known to have hepatotoxic property), 111 mg (or 0-1500mg) of methionine, 23.1mg (or 0-1000mg) of niacinamide (also commonly known as nicotinamide or vitamin B3) and 180mcg (or 0-250 mcg) of folic acid (see Tables 1 and 2), wherein said composition is prepared in suitable dosage forms including oral, parenteral, rectal and topical forms (column 3, lines 65-67 and claims 1 and 3).

Since the interpretation of the instant claims allows for the inclusion of any other unspecified ingredients even in major amounts in said composition, Summers anticipates the instant invention.

With respect to the limitations in claims 3-6 and 9-12, the referenced parenteral administration (Webster's II dictionary defines the term "parenteral" as "taken into the body or

administered in manner other than through the digestive tract, as by intravenous or intramuscular injection") "metes and bounds" the instantly claimed "solutions, suspensions...", "injection", "sterile solutions or suspensions" or "...intramuscular, intravenous...". Therefore, Summers anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroger et al. (Gen. Pharmac., Vol. 28, No. 2, pp. 257-263, 1997) and further in view of Yang (US 5474757).

Kroger teaches use of combination of nicotinamide (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) and methionine (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) in decreasing hepatotoxicity induced by the hepatotoxic compound such as 500mg/kg of acetaminophen (abstract; Figure 2; Results; Discussion).

Yang teaches a composition comprising acetaminophen, organosulfur compound and methionine (claims 17 and 21), wherein said acetaminophen is present in dosage amounts of "from 0.04 mg/kg/day to about 50 mg/kg/day" in various dosage forms including tablets, gelcaps, capsules, caplets, granules, solution, suspension or injectable forms, for example "80mg, 325mg, 500mg, and 650mg" in oral solid dosage forms, "100 mg/ml, 120 mg/2.5 ml, 120 mg/5 ml, 160 mg/5 ml, 165 mg/5 ml, 325mg/5 ml" in oral liquid dosage forms (column 9, line 5 thru column 10, line 11); . Yang teaches the use of methionine as protective agent for acetaminophen overdose (column 2, lines 4-6; claims 17 and 21).

Kroger differs from the claimed invention in the preparation of a composition comprising acetaminophen, nicotinamide and methionine in the specific amounts, namely about 80-1000 mg dose of acetaminophen, about 5 mg to about 500 mg dose of methionine and about 10 mg to about 500 mg dose of nicotinamide, per standard dose.

However, it would have been prima facie obvious, within the meaning of 35 USC 103, to employ the components in combination for their known functions. One having ordinary skill in the art would have expected as based upon the prior art and the fact that each of the three components of the composition used in the claimed invention is conventionally employed in the art for reducing acetaminophen overdose hepatotoxicity.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the determination of the specific dosage amounts of each ingredient in said composition, those of ordinary skill in the art would have been readily optimized effective dosages as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose would have been calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed in the prior art references.

Conclusion

10. No Claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
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